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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/147,036	12/15/1998	JOCHEN MAURER	P564-8019	1165

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	28

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/147,036	Applicant(s) MAURER ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 41, 43-59* is/are pending in the application.

4a) Of the above claim(s) *4-8 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9-19,41,43-53 and 55-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed January 23, 2003. Claim 1 has been amended.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Objections/Rejections Withdrawn

3. In view of Applicant's amendment and response the following rejections are withdrawn:

a) Objection to the Drawings, page 3, paragraph 4 of the previous Office action.
b) Rejection of claims 1-2, 9-10 and 15-19 under 35 U.S.C. 102(b), pages 5-6, paragraph 6 of the previous Office action.
c) Rejection of claims 1-3, 9-10, 41 and 43-59 under 35 U.S.C. 103(a), pages 7-9, paragraph 7 of the previous Office action.

Objections/Rejections Maintained

4. The rejection of claims 1-2, 9-10 and 15-19 under 35 U.S.C. 102(b) as being anticipated by Georgiou et al is maintained for the reasons set forth on pages 3-6, paragraph 5 of the previous Office Action.

The rejection was on the grounds Georgiou et al teach a method for producing stable, surface-expressed polypeptides from recombinant gram-negative bacterial cell hosts. Georgiou et al teach that the invention comprises chimeric genes which include a targeting DNA sequence encoding a polypeptide capable of targeting and anchoring the fusion polypeptide to a host cell outer membrane (column 3, lines 53-57), a traversing sequence capable of transporting a heterologous or homologous polypeptide

through the outer membrane (column 4, lines 4-14) and a DNA segment that encodes any one of a variety of desired polypeptides (column 4, lines 31-33). Georgiou et al teach that the chimeric gene when provided with a functional promoter is expressible in gram-negative host (column 4, lines 34-37). Georgiou et al teach that the recombinant vectors of the invention will express fusion polypeptides and will include a functional promoter sequence and a targeting DNA sequence encoding a protein capable of targeting to the outer surface of a gram-negative bacterial host cell (column 4, lines 38-46). Georgiou et al teach that DNA sequences used in the invention may be fused via a polylinker region (column 5, line 1-2). Georgiou et al teach that the transporter sequence of the invention may be derived from a membrane spanning domain of suitable length from any native outer membrane protein of gram-negative bacteria including outer membrane proteins such as OmpT, FepA and the like (column 5, lines 49-51). Therefore, the protease recognition site would be intrinsic or naturally present in the host cell.

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Georgiou et al do not disclose a polynucleotide comprising a nucleotide sequence that encodes a transporter domain located downstream from a nucleotide sequence that encodes a passenger peptide.

Applicant's arguments filed January 23, 2003 have been fully considered but they are not persuasive. The Examiner disagrees with Applicant's assertion that "Georgiou et al does not disclose a polynucleotide comprising a nucleotide sequence that encodes a transporter domain located downstream from a nucleotide sequence that encodes a passenger peptide". Georgiou et al teach that a particular embodiment of the invention includes recombinant vectors that include a functional promoter sequence and a targeting DNA sequence encoding a protein capable of targeting to the outer surface of a gram-negative bacterial host cell. Georgiou et al teach that the targeting gene

sequence is typically positioned downstream of the promoter sequence. Georgiou et al teach that the transmembrane will encode a protein domain capable of transversing the cell outer membrane and the vector will also include DNA sequence which encodes a desired protein. Georgiou et al teach that this sequence when positioned downstream of the transmembrane sequence will be expressed on the external surface of the outer membrane, and typically is exposed to the external medium while remaining stably anchored to the membrane surface (column 4, lines 38-57). Therefore, Georgiou et al teach a DNA segment that encodes a transmembrane protein that is downstream from the targeting sequence. It is the Examiner's position that there is nothing of the record to show why the method of the reference is not the same as the claimed method.

5. The rejection of claims 1-3, 9-10, 15-16, 41, 43-53 and 55-59 under 35 U.S.C. 103(a) as being unpatentable over Georgiou et al in view of Benz et al is maintained for the reasons set forth on pages 9-10, paragraph 8 of the previous Office Action.

The rejection was on the grounds that Georgiou et al teach a method for producing stable, surface-expressed polypeptides from recombinant gram-negative bacterial cell hosts. Georgiou et al teach that the invention comprises chimeric genes which include a targeting DNA sequence encoding a polypeptide capable of targeting and anchoring the fusion polypeptide to a host cell outer membrane (column 3, lines 53-57), a traversing sequence capable of transporting a heterologous or homologous polypeptide through the outer membrane (column 4, lines 4-14) and a DNA segment that encodes any one of a variety of desired polypeptides (column 4, lines 31-33). Georgiou et al teach that the chimeric gene when provided with a functional promoter is expressible in gram-negative host (column 4, lines 34-37). Georgiou et al teach that the recombinant vectors of the invention will express fusion polypeptides and will include a functional promoter sequence and a targeting DNA sequence encoding a protein capable of targeting to the outer surface of a gram-negative bacterial host cell (column 4, lines 38-46). Georgiou et al teach that DNA sequences used in the invention may be

fused via a polylinker region (column 5, line 1-2). Georgiou et al teach that the transporter sequence of the invention may be derived from a membrane spanning domain of suitable length from any native outer membrane protein of gram-negative bacteria including outer membrane proteins such as OmpT, FepA and the like (column 5, lines 49-51).

Georgiou et al do not teach AIDA protein.

Benz et al teach that AIDA-I has been identified as the adhesin which mediates the diffuse adherence phenotype of enteropathogenic *E. coli* (page 1543, 1st column). Benz et al teach that the N-terminus amino acid sequence derived from the nucleotide sequence of ORFB after cleavage presents a signal peptide of 49 amino acids (page 1543, 2nd column). Benz et al teach that after cleavage of the signal peptide further processing occurs at the C-terminus of the AIDA-I precursor (page 1543, 2nd column). Benz et al suggest that this cleavage step is part of the transport mechanism to the outer membrane, a similar processing step was shown to be involved in maturation of the IgA protease of *Neisseria gonorrhoeae* (page 1543, 2nd column).

It would be *prima facie* obvious to one of ordinary skilled in the art at the time the invention was made to add the transporter domain of the AIDA-I protein as taught by Benz et al to the host bacterium used in the method for producing stable, surface-expressed polypeptides from recombinant gram-negative bacterial cell hosts of Georgiou et al because Benz et al suggest that the cleavage step that occurs at the C-terminus of the AIDA-I precursor is part of the transport mechanism to the outer membrane, a similar processing step was shown to be involved in maturation of the IgA protease of *Neisseria gonorrhoeae* (page 1543, 2nd column).

Applicant directs the Examiner to the previous arguments regarding Georgiou et al. Applicant urges that Georgiou et al fail as a primary reference and Benz et al do not cure the deficiencies of Georgiou et al. Applicant urges that Georgiou et al and Benz et al do not teach or suggest the process invention as a whole. Applicant urges that Georgiou et al in combination with Benz et al do not teach the inventive vector nor do they teach the process using the vector to obtain a recombinant bacterial library. Applicant urges that Georgiou et al in combination with Benz et al do not teach a recombinant bacterial cell.

Applicant's arguments filed January 23, 2003 have been fully considered but they are not persuasive. The claims are directed to a process for presenting passenger

peptides or polypeptides on the surface of gram-negative bacteria. Georgiou et al teach a method for producing stable, surface-expressed polypeptides from recombinant gram-negative bacterial cell hosts. Georgiou et al teach that the invention comprises chimeric genes which include a targeting DNA sequence encoding a polypeptide capable of targeting and anchoring the fusion polypeptide to a host cell outer membrane (column 3, lines 53-57), a traversing sequence capable of transporting a heterologous or homologous polypeptide through the outer membrane (column 4, lines 4-14) and a DNA segment that encodes any one of a variety of desired polypeptides (column 4, lines 31-33). Georgiou et al do not teach AIDA protein. However, Benz et al teach that AIDA-I has been identified as the adhesin which mediates the diffuse adherence phenotype of enteropathogenic *E. coli* (page 1543, 1st column). It would have been obvious to add the transporter domain of the AIDA-I protein as taught by Benz et al to the host bacterium used in the method for producing stable, surface-expressed polypeptides from recombinant gram-negative bacterial cell hosts of Georgiou et al because Benz et al suggest that the cleavage step that occurs at the C-terminus of the AIDA-I precursor is part of the transport mechanism to the outer membrane, a similar processing step was shown to be involved in maturation of the IgA protease of *Neisseria gonorrhoeae* (page 1543, 2nd column). The Examiner disagrees with Applicants assertion that "Georgiou et al in combination with Benz et al do not teach the inventive vector nor do they teach the process using the vector to obtain a recombinant bacterial library". Georgiou et al discloses and describes a gene segment encoding a desired polypeptide which are selected and inserted by the method of the invention into one or more

recombinant vectors (column 6, lines 47-52) and Georgiou et al also discloses that numerous types of fusion polypeptides may be expressed using the transport system (column 6, lines 19-20). Therefore, one of ordinary skill in art would reasonably conclude that the process using the recombinant vector could be used to obtain a recombinant bacterial library. Applicant is referred to the Examiner's comments above (paragraph 4) regarding Georgiou et al regarding their assertion that Georgiou et al is not a primary reference. There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

6. The rejection of claims 1-3, 9-19, 41, 43-53 and 55-59 under 35 U.S.C. 103(a) as being unpatentable over Georgiou et al in view of Benz et al and further view of Kozono et al is maintained for the reasons set forth on pages 11-2, paragraph 9 of the previous Office Action.

The rejection was on the grounds that Georgiou et al and Benz et al have been described previously.

Georgiou et al and Benz et al as combined *supra* do not teach a passenger polypeptide that is an antibody or antigen-binding domain of antibody.

Kozono et al teach a MHC class II protein with covalently bound single peptides (see the Title). Kozono et al teach that MHC class II proteins by genetically attaching the peptide by a flexible peptide linker to the linker to the amino terminus of the class II β chain. Kozono et al teach that the peptide is engaged by the peptide binding groove of the secreted MHC molecule and this complex is recognized by T cells receptors specific for that combination (see the Abstract). Kozono et al suggest that the peptide covalently attached to the N-terminal of the β chain of the class II could lie within the peptide-binding groove of the molecule (page 151, 1st column).

It would be *prima facie* obvious at the time the invention was made to add the MHC class II protein with covalently bound single peptides as taught by Kozono et al to fusion polypeptides of Georgiou et al because Kozono et al teach that the peptide is engaged by the peptide binding groove of the secreted MHC molecule and this complex is recognized by T cells receptors specific for that combination and may also allow very efficient induction of tolerance in vivo to particular class II/peptide complexes, a

phenomenon that may be of therapeutic significance (page 154, 2nd column). It would be expected barring evidence to the contrary, that the addition of the MHC class II protein with covalently bound single peptides as taught by Kozono et al to the fusion polypeptides used in the method for presenting passenger peptides or polypeptides on the surface of gram-negative host bacteria of Georgiou et al would be invaluable in studies of positive selection of T cells.

Applicant urges that Georgiou et al fail as a primary reference and Benz et al do not cure the deficiencies of Georgiou et al. Applicant urges that Kozono et al do not teach or suggest the essential features of the invention and therefore does not cure the deficiencies of Georgiou et al and Benz et al.

Applicant's arguments filed January 23, 2003 have been fully considered but they are not persuasive. The claims are directed to a process for presenting passenger peptides or polypeptides on the surface of gram-negative bacteria. The teachings of Georgiou et al and Benz et al have already been disclosed above. Kozono et al teach fusion proteins between MHC Class II proteins and a peptide attached by a flexible peptide linker (which is described in the specification on page 27). It would be obvious to add the MHC class II protein with covalently bound single peptides as taught by Kozono et al to fusion polypeptides of Georgiou et al and Benz et al combined because Kozono et al teach that the peptide is engaged by the peptide binding groove of the secreted MHC molecule and this complex is recognized by T cells receptors specific for that combination and may also allow very efficient induction of tolerance *in vivo* to particular class II/peptide complexes (a phenomenon that may be of therapeutic significance). It should be noted that the specification teaches the use of fusion proteins that could be expressed on the surface of *E. coli* (page 27 of the specification).

Therefore, the fusion proteins of Kozono et al could be used in the claimed method. Applicant is referred to the Examiner's comments above (paragraph 4) regarding Georgiou et al regarding their assertion that Georgiou et al is not a primary reference. Applicant is also referred to the Examiner's comments above (paragraph 5) regarding their assertion that Benz et al not curing the deficiencies of Georgiou et al. There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
April 10, 2003

NITA MINNIFIELD
PRIMARY EXAMINER
4-17-03